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ABSTRACT

The role of pharmacologic agents in the treatment of learning and behavior disorders in children is discussed with respect to the biological basis of these disorders. Illustrative studies dealing with autonomic reactivity and cortical excitability as reflected in the cortical evoked response are presented. The question of the combined effects of drug and behavioral or educational therapies is considered. The author makes a plea for a comprehensive theoretical viewpoint in the consideration of learning and behavior disorders, not neglecting the biologic contributions of these problems and the possible benefits of combining environmental and pharmacologic treatments. (Author)

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# PSYCHOACTIVE DRUGS FOR CHILDREN:

# STATUS AND POTENTIAL

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Paper presented at the American Educational Research Association Annual Meeting, Boston, MA, April 7, 1980.

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It is no longer possible to think of the developing human organism as either an independent physio-chemical system developing along fixed biologic trajectories, or as a uniformly constituted entity whose behavior is largely the effect of environmental contingencies. Brain and social ecology are clearly mutually interdependent reference points for understanding human behavior. It is true, of course, that if one holds variation of brain function constant, then behavior will be explicable almost solely in terms of variables such as family environment, educational experience, and social interaction. Equally, holding social environment constant, behavior will be seen to vary as a function of biologic endowment variables, including genetic influences, individual variations in structure, and insults to biologic integrity. Bio-medical and socio-behavioral methodologies are complementary means of envisioning the total process of human development and function.

I make these philosophical comments because I am mindful of the deep and persistent urge, particularly amongst educators and social theoreticians, to explain all of human behavior from one perspective only, namely that of the malleable human infant whose behavior is totally explicable in terms of the experiences which it incurs in the process of socialization and education. When challenged at a purely theoretical level, most will of course admit the reality of biologic influences. No one, save those who eschew scientific models altogether, denies that the brain is the organ of behavior, in much the same way that the heart is the organ of circulation: although many external factors influence the rate, rhythm and capacity of the heart, including changes in the environment, without the heart, blood

ceases to circulate and sustain life. Likewise, without the brain, behavior does not occur at all, and alterations of the brain produce profound alterations in behavioral capacities.

Moreover, the brain itself, though an anatomical structure evolved according to fixed genetic rules, develops within wide limits, dependent upon the environment for the final ways in which it becomes organized and differentiated. It cannot, in other words, be understood fully without reference to the context in which it develops.

Having said this, and perhaps having agreed upon these basic assumptions, the emotional urge to deny the role of the brain in behavior will not go away. Confronted with specific examples in which behavior is jointly influenced by both biologic and social variables, many will resort to elaborate denials of this fundamental reality. The ease with which pompous moralizing and curiously simplistic thinking enters the arena is astonishing. Journalists become instant experts, proclaiming the "myth" of hyperkinesis; or instant epidemiologists, announcing in frightening terms the mass subjugation of exuberant youth to the evils of pharmacology. They are helped along by shallow social analysts who first seize upon the so-called "data" proclaimed by the journalists, and then pronounce judgment on "the medicalization of deviancy", as though all deviant behavior is solely and axiomatically a social problem.

In order to envision the proper role of psychoactive drugs for children, we must first free ourselves of these emotional prejudices, and accept some basic assumptions regarding brain and behavior. First, we must

assume that the brain can misfunction, either as a whole, or more frequently, in certain specific ways. Secondly, we must assume that not all such dysfunctioning is remediable by environmental or educational alternatives. Thirdly, we must assume that there are interactive effects, such that improvement of both brain function and environment leads to better outcome than improvement of only one of the factors. Finally, we must accept the fact that both biologic and social remediation of dysfunction have side effects, and that the cost/benefit ratio determines the social utility of the treatments.

Disorders of Learning and Behavior: Biological Correlates

The early history of a biologic approach to learning was focussed upon children who had sustained clear cut brain injury, such as children with cerebral palsy and those exposed to toxic encephalitic infections. These conditions are associated with profound uneveness of cognitive and behavioral function, and require sustained educational and environmental interventions. Neurologic dysfunction thus became the model for understanding disorders of behavior and learning. The association of obvious motor neurologic dysfunction with the cognitive and behavioral dysfunctions led some to assume that the latter were invariably a sign of the former, the error of post hoc, ergo proper hoc. The large NINDS collaborative perinatal study which followed over 50,000 normal women from pregnancy until seven years of age, showed that these neurologic signs are a separate factor which do relate to later learning disabilities, but only rather weakly. Similarly, the longitudinal studies of Werner and colleagues on the island of Kauai, Hawaii, show some predictability to

later learning dysfunctioning. But not all brain dysfunction is evident in neurologic motor abnormalities; nor do the presence of such abnormalities invariably relate to disturbed learning.

In addition to these "structural" approaches to brain influences on learning, more recent investigations have sought to elucidate the role of physiologic factors in learning. I will describe only two: autonomic and cortical response to information processing demands.

It became clear quite early that many children with profound disturbances of learning and behavior did not have overt neurologic signs of brain damage, and it therefore seemed reasonable to look for signs of disturbed function in the brain. The single most important clue about this disturbed function came from the serendipitous finding of Bradley regarding the influence of Benzedrine on children hospitalized for severe disturbances of learning and behavior. Amphetamines are sympathomimetics; that is, they mimic the action of the sympathetic nervous system, much as the naturally occurring hormone adrenalin (epinephrine) does in the peripheral nervous system. Epinephrine and amphetamine energize the peripheral sympathetic nervous system, just as in the brain itself they facilitate the transmission of neural impulses. This activation effect suggests that the disorders of learning and impulse control might have a common relationship to central activation mechanisms.

In one of the first studies on this subject, Gerard Rothschild and I showed that amphetamine enhances the rate at which the autonomic nervous system adapts to the activation produced by series of tones among

hyperkinetic children treated with amphetamine. Figure 1 shows the effect

Figure 1 here

of a soft 750 Hz tone on finger pulse volume and galvanic skin response. Figure 2 shows the very different rate at which the hyperkinetic child adapts compared with his normal sibiling to a series of 14 tones. Note that when a new tone is presented, the normal response is

Figure 2 here

increased activation, whereas the hyperkinetic child shows a lack of responsiveness. Similarly, if one asks the hyperkinetic child to respond to a simple "go-no go" task (press a button when you see the dim flash, but not the bright one), finger pulse volume and GSR show virtually no difference in level of arousal to the two types of stimuli (Figure 3).

Figure 3 here

At the cortical level we can make use of one of the supremely elegant advances of modern neurophysiology, the cortical evoked potential. By computer averaging of the electrical brain responses following repeated stimulation, one can extract the specific response of the brain from the ongoing noise which normally obscures the potentials which occur during the

specific information processing tasks. Figure 4 shows a family of

Figure 4 here

children with reading disorders, all four siblings being severely impaired in reading, as were the father, uncle and paternal grandmother. We examined the visual evoked potentials of this family, and found a markedly attenuated potential in the left side of the area of the scalp lying near the centers where auditory and visual information are thought to be integrated in language decoding (Wernicke's area).(Figure 5)

Figure 5

These findings are meant to be illustrative only. Vigorous research continues in the effort to document the relationship between measurable brain dysfunction and learning functions such as reading. Similarly, considerable work now shows that children without learning problems, but with severe problems of impulse control, show deficiencies which can be detected in these measures of brain function. Specifically, it can be shown that hyperkinetic children show deficiencies in both arousal processes and selective attention processes, and that these deficiences can be detected by the cortical evoked potential.

I mention these physiological investigations in order to underline my

earlier point, that deviations of behavior and learning invariably involve rather specific activities of the brain, and in some cases we are fortunate enough to have a tool which gives us a window through which we can see perhaps only dimly, some of the brain's working at a physiological level. It is through such methods that we can then proceed to our topic of interest, the role of drugs in affecting behavior and learning. It is only by such knowledge that a rational psychopharmacology of children can be developed. Until this time, the treatments have been based entirely upon empirical guidelines.

Drug Effects On Behavior and Learning

If we give a drug like amphetamine for the correction of some dysfunctioning brain activity, it behooves us to demonstrate that the brain function in question is actually altered in a way we can understand. For example, Figure 6 shows the effect of amphetamine and pemoline (Cylert) upon the evoked potentials under conditions where the subject attends to a relevant stimulus or merely receives an irrelevant flash. These data

Figure 6 here

suggest to us that it is the attention mechanism that is being affected by these stimulant drugs. When the child is required to attend and do something with the information (press a key), he must both attend to the relevant aspects of the stimulus, and inhibit irrelevant responding. Both of these functions, arousal and inhibition, appear to be markedly altered

by stimulant drugs, in normal children as well as hyperkinetics. By now the stimulant drugs have been shown to have extremely clear and replicable effects across a wide variety of tasks, both cognitive and behavioral (Figure 7 ). It is generally believed that these changes are secondary to

Figure 7 here

fundamental changes taking place in brain mechanisms subserving arousal and selective inhibition, possibly in the reticulo-frontal areas of the brain.

Comparative Treatment Studies

The literature may be divided into those studies comparing drug therapy with controls (usually placebo treated children); and those comparing two or more active treatments. Virtually no good studies have shown a failure of the stimulant drugs to improve cognitive and behavioral functions in comparison with placebos. Various other drugs, including sedatives, tranquilizers, anti-epileptics such as Dilantin and Zarontin, and various stimulants have been compared with amphetamine or methylphenidate (Ritalin). Methylphenidate, dextro- and levo-amphetamine, and pemoline (Cylert) show approximately the same effects in a number of carefully controlled double-blind trails. Caffeine, though centrally active, has not been found effective, nor have the other drug classes.

Other therapies have included special education, behavior therapy, cognitive therapy, and biofeedback. Most of these studies do not meet

rigorous methodologic standards, but two important comparisons have been made with behavior therapy. In the first, Gittelman-Klein and associates compared methylphenidate, behavior therapy, and methylphenidate plus behavior therapy in terms of direct measures of classroom behavior. They found that both behavior therapy and methylphenidate improved behavior significantly above control levels, but that the combination was no better than methylphenidate alone.

In another important study, Loney et al. showed that the combination of methylphenidate and classroom behavior therapy gave better results than either alone. Relatively little is known about a longer course of drug and nondrug therapies in combination since most comparisons have been of two or three month duration only.

However, recently Satterfield has reported that both behavioral and learning functions were maintained at near-normal rate in a group of children given an optimal treatment program of drugs, psychotherapy, educational intervention, or whatever the particular individual case seemed to require. This "multi-modality" approach in which several treatments are combined in accord with the individual patient's needs, more closely approximates the realities of therapy than the single method approaches that have been tried so far. This approach nautrally poses a greater challenge to research methodology than the simple random-groups designs previously used by most investigators.

Side effects

Most side effects are dose-related. At high doses almost all drugs produce physiological changes that may be unwanted and unpleasant. With the stimulant drugs, the two most prominant side effects are anorexia and insomnia. Both are controllable by appropriate dose and schedule adjustment. Figure 8 shows the typical course of these side effects in a

Figure 8 here

study of pemoline and dextroamphetamine. On the whole, the stimulants are quite benign in terms of immediate side effects. In the long term, it has been shown that high doses of the stimulants may cause a temporary slight decrement in linear growth. But this effect has been examined carefully and found to be be a temporary growth suppression which disappears after one or two years during treatment, with the children reaching levels consonant with their expected development.

New Developments

Although little has yet been done, recent interest centers on an entirely new class of drugs which appear to have little or no apparent physiological side effects, but which may exert profound influence on verbal learning and other intellective functions. Figure 9 shows results

Figure 9 here

of a study on university undergraduates with treatment by a drug called

Piracetam, one of the so-called "nootropic drugs", or learning drugs. This particular agent is thought to enhance transmission across the corpus callosum (connecting the two hemispheres of the brain), to produce a kind of "superconnection syndrome". As we learn more of the pharmacology and physiology of brain function, we may be sure that chemical control over high level brain functions will become a reality.

Conclusions

We conclude that where there is demonstrable brain dysfunction, there is also a potentially useful form of treatment. Based upon knowledge of the chemical and functional interrelationships in the brain one should be able to select that combination of chemical and environmental changes which optimizes the behavior and learning of the child whose brain does not function normally. Most of the fears and prejudices against such treatments do not have a factual basis, though undoubtedly as with all technology this one is subject to mis-use. Correcting a dysfunction, whether due to genetic or exogenous interference with normal processes, must be weighed against the possible alternatives. Among these are the dangers of being untreated, or treated ineffectively. Long term studies now show that severe behavioral and learning disturbances lead to very poor outcomes in emotional, social, and vocational respects. Adequate investigation of sustained optimal treatments have not been done, although short-term studies indicate what might be accomplished.

Whether an entirely new class of drugs which enhance normal functioning will be forthcoming is not clear, but seems likely given the ingenuity of

science and the drive towards perfectibility which has characterized the human species. If such drugs appear, then entirely new questions regarding the role of drugs and behavior will have to be answered.

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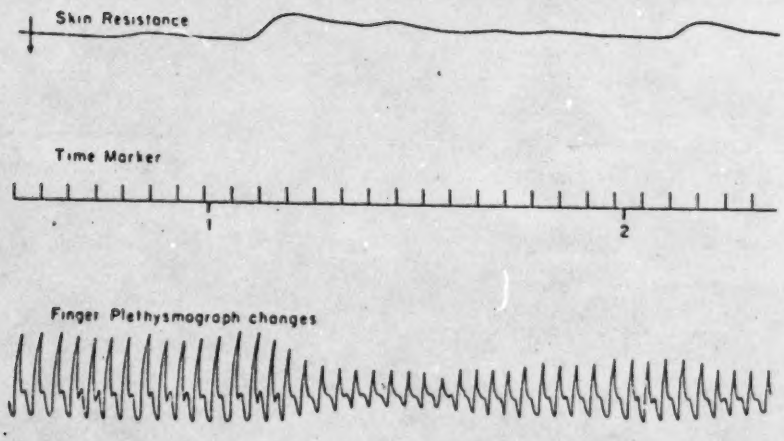

Skin Resistance
Time Marker
1
2
Finger Plethysmograph changes

Figure 1

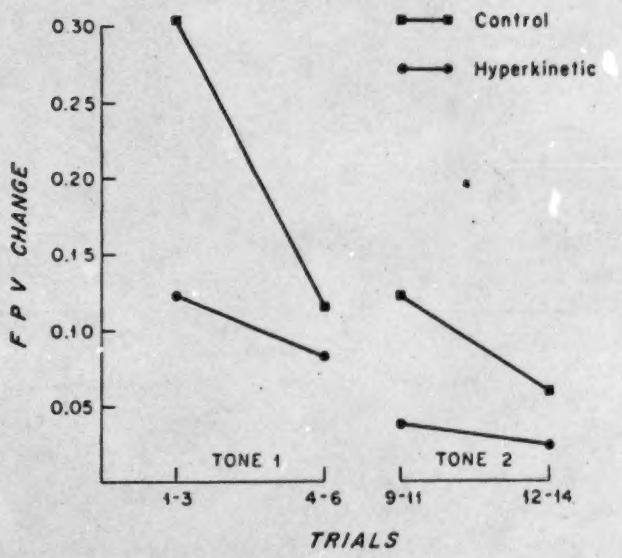

Control
Hyperkinetic
0.30
0.25
0.20
0.15
0.10
0.05
F P V CHANGE
TONE 1
TONE 2
1-3
4-6
9-11
12-14
TRIALS

Figure 2

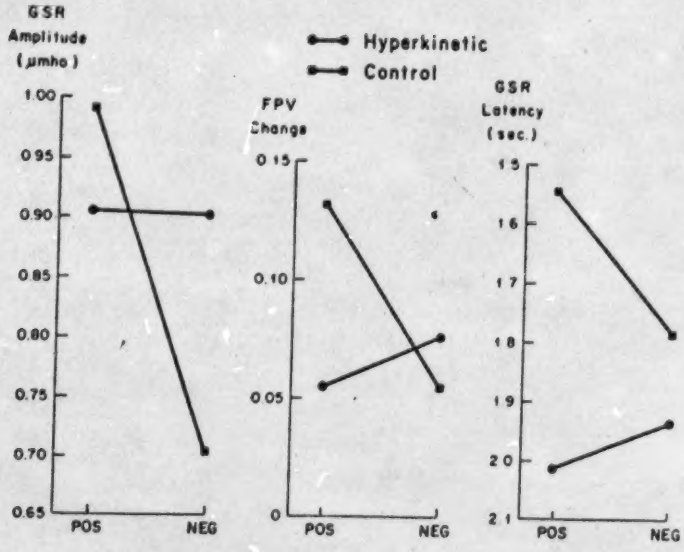
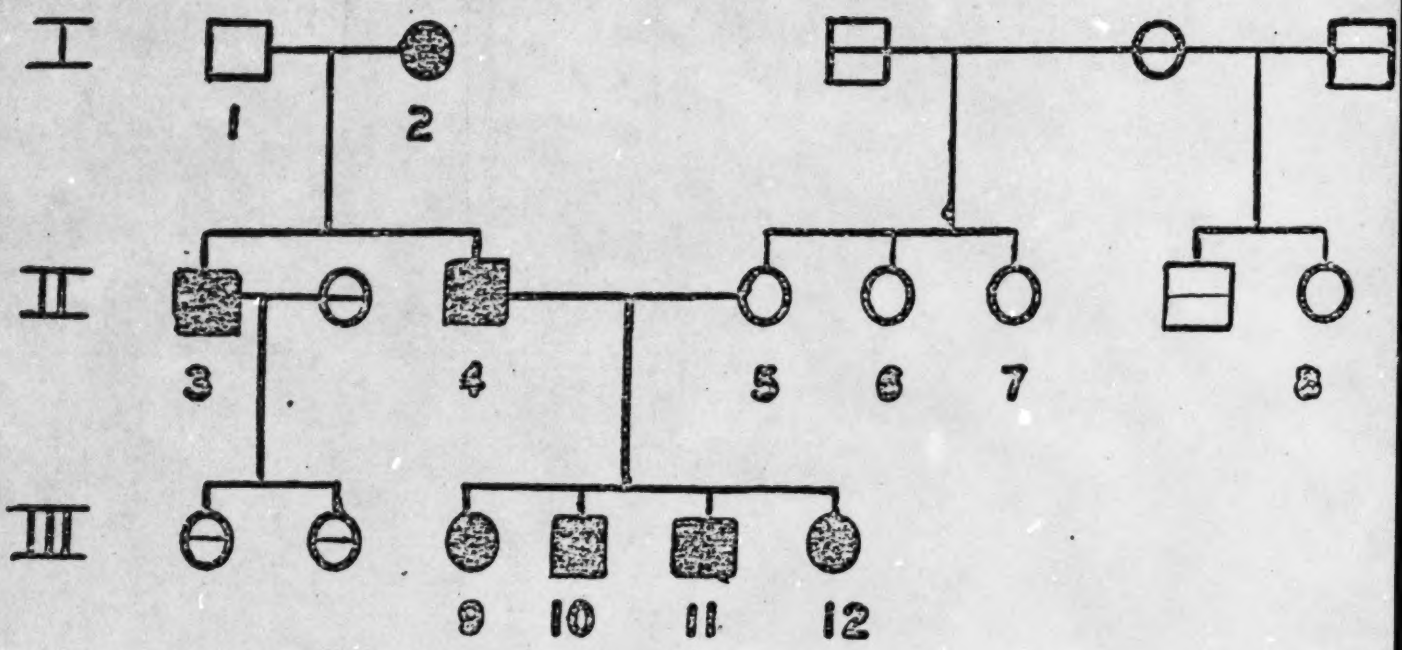

GSR
Amplitude
(μmho)
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
POS
NEG
Hyperkinetic
Control
FPV
Change
0.15
0.10
0.05
0
POS
NEG
GSR
Latency
(sec.)
1.5
1.6
1.7
1.8
1.9
2.0
2.1
POS
NEG

Figure 3

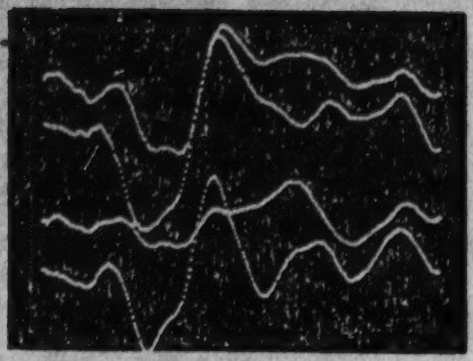



TESTED READING DISABILITY

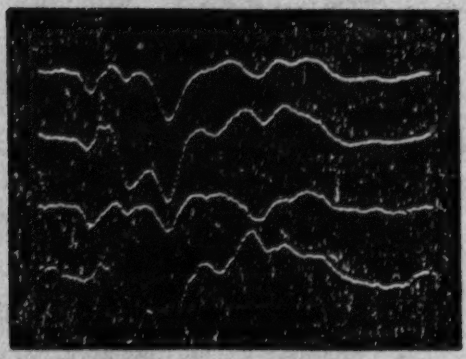
TESTED ADEQUATE READER

UNTESTED

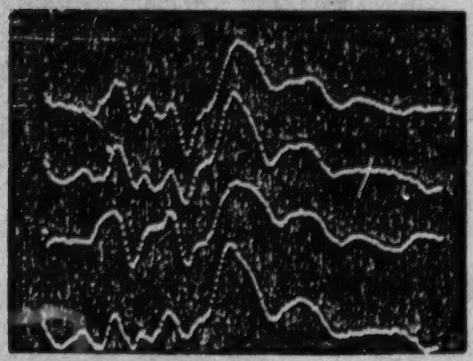
Figure 4



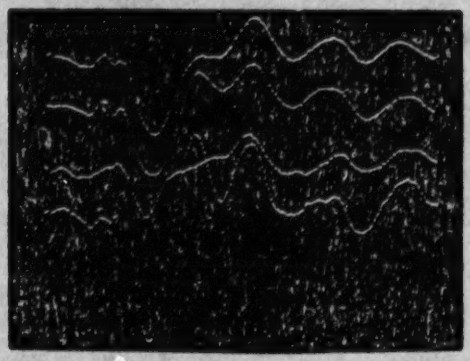
INDEX CASE
MALE AGE 11-6



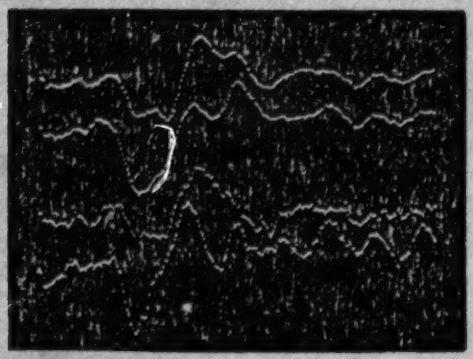
SISTER
AGE 15-0



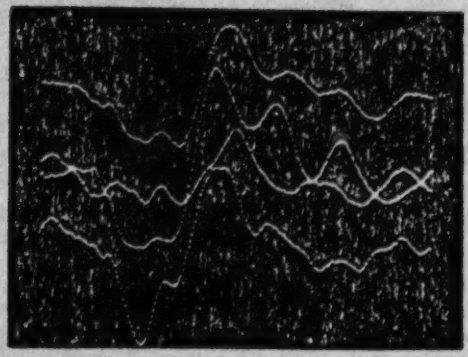
FATHER
AGE 37-3



BROTHER
AGE 13-8



MOTHER
AGE 36-9



SISTER
AGE 9-9

VISUAL EVOKED RESPONSE IN FAMILY WITH READING DISORDER. CURVES TOP TO BOTTOM ARE LEFT OCCIPITAL, RIGHT OCCIPITAL, LEFT PARIETAL AND RIGHT PARIETAL.

Figure 5

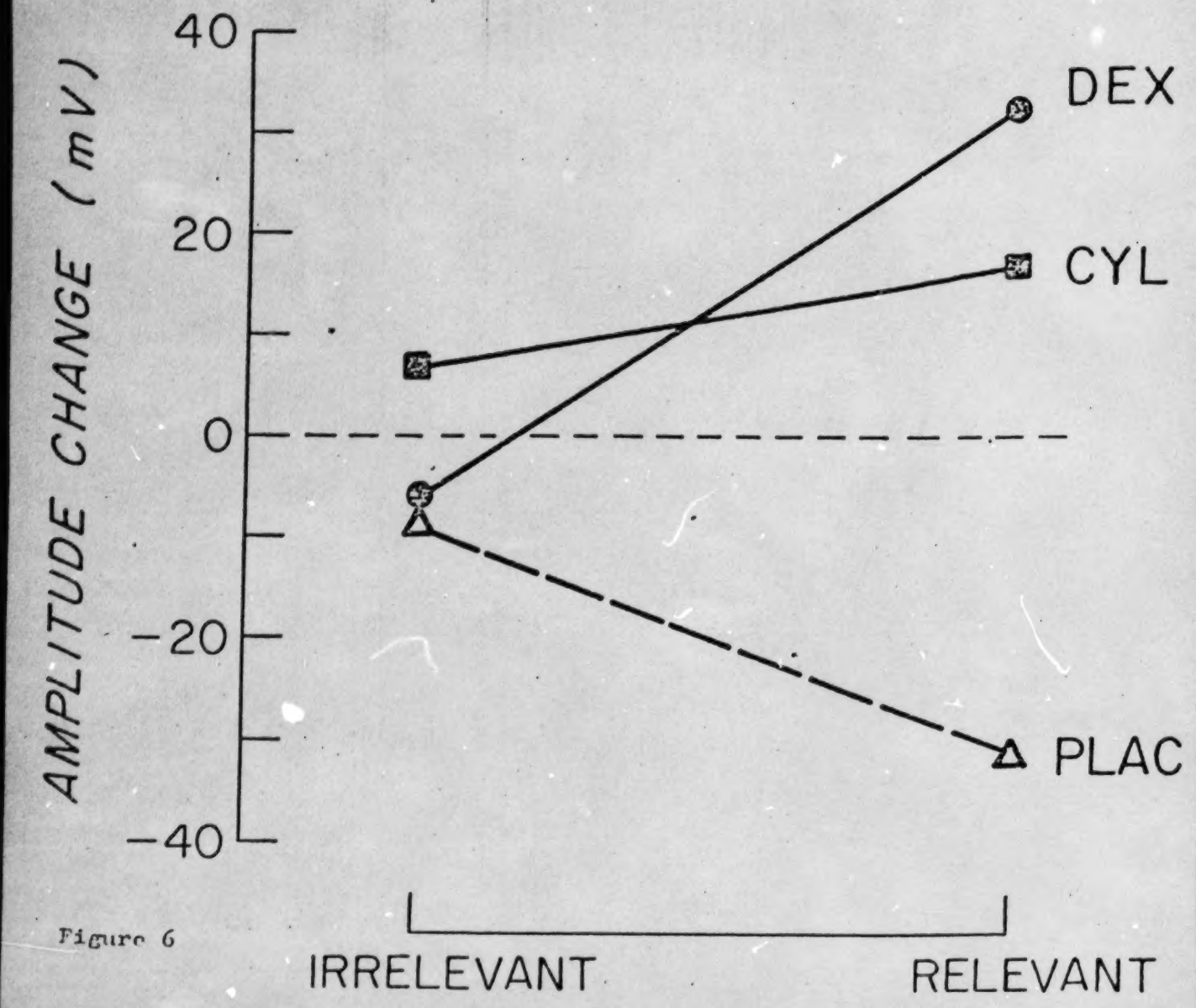

AMPLITUDE CHANGE (mV)
40
20
0
-20
-40
DEX
CYL
PLAC
IRRELEVANT
RELEVANT

Figure 6

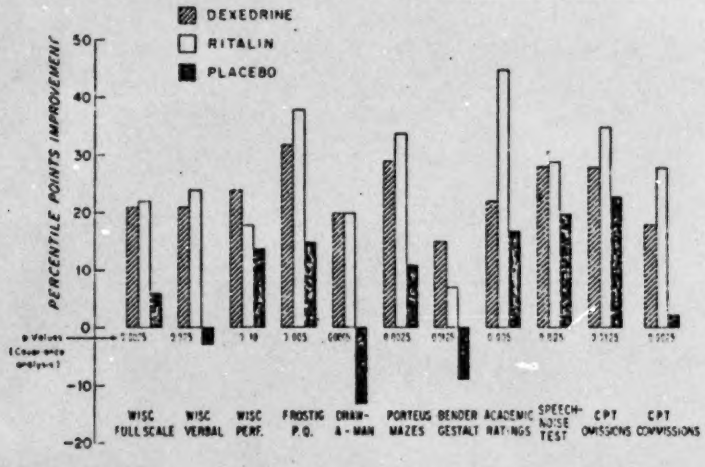

DEXEDRINE
RITALIN
PLACEBO
PERCENTILE POINTS IMPROVEMENT
50
40
30
20
10
0
-10
-20
WISC FULL SCALE
WISC VERBAL
WISC PERF.
FROSTIG P.Q.
DRAW-A-MAN
PORTEUS MAZES
BENDER GESTALT
ACADEMIC RATINGS
SPEECH-NOISE TEST
CPT OMISSIONS
CPT COMMISSIONS

Figure 7

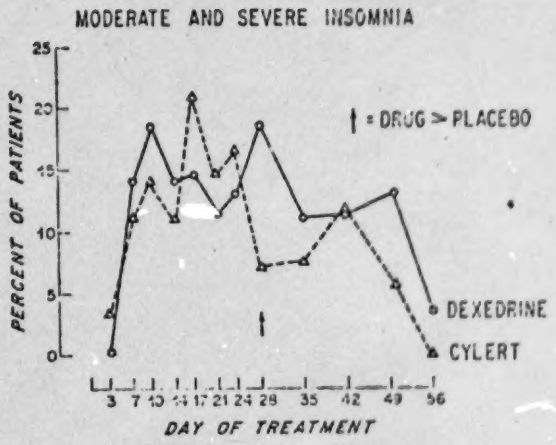

MODERATE AND SEVERE INSOMNIA
PERCENT OF PATIENTS
25
20
15
10
5
0
↑ = DRUG > PLACEBO
DEXEDRINE
CYLERT
3 7 10 14 17 21 24 28 35 42 49 56
DAY OF TREATMENT

Figure 8

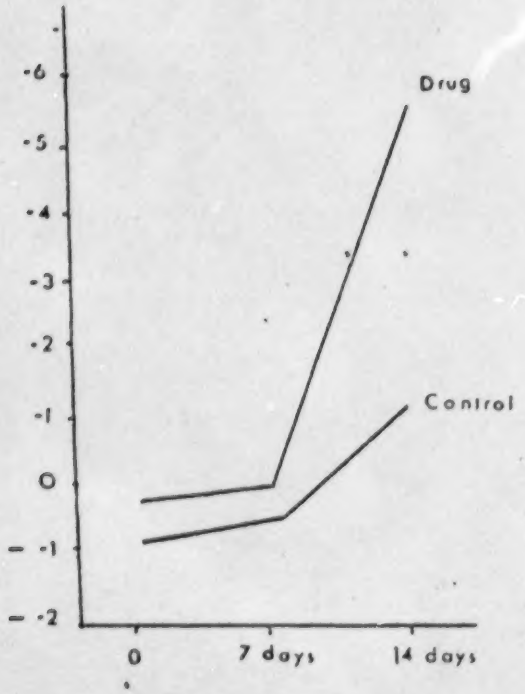



Figure 9